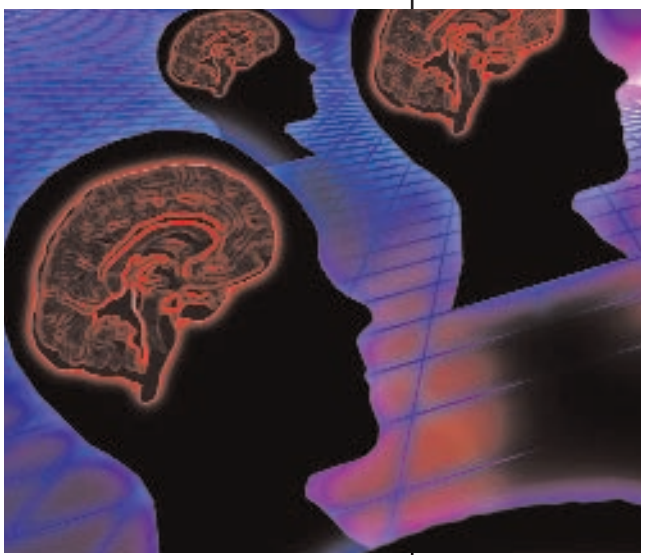
BLOOD-BRAIN BARRIER AND ALZHEIMER'S



...a dysfunction of the blood-brain barrier could induce abnormal transport of A beta from sera and accumulation into the CNS, playing a critical role in the development of Alzheimer's disease.

DEAR EDITOR:

The blood-brain barrier (BBB) was discovered when dyes, injected into living animals, stained all tissues except for most of the brain and spinal cord, leading to the postulated BBB. The BBB is a physiologic matrix of tissue that is selectively permeable and protective of the central nervous system (CNS). The BBB is located within the endothelium of cerebral capillaries and the choroids plexus epithelium. The BBB preserves concentrations within the CNS through reciprocal homeostatic processes. The rate with which substances penetrate through to the brain tissue is inversely related to their molecular size and directly related to their lipid solubility. The factors that are responsible for transfer across the capillary partition include vesicular transport, diffusion, and filtration. Diffusion is quantitatively more important in terms of exchange of nutrients and waste materials. Filtration depends upon a balance of forces between hydrostatic and osmotic pressure gradients.[1–7]

BBB integrity can be compromised by hypertension, cerebrovascular ischemia, histologic and metabolic changes within barrier tissue cells, vascular disease, systemic metabolic disease, trauma, tumors, medications, noxious stimulation, infection, irradiation, transport and permeability alterations, and aging. Common central disease states involving BBB integrity include Binswanger's Disease, periventicular hyperintensities, ischemic cerebrovascular events, hypoxia-ischemia, septic encephalopathy, reactionary inflammatory mechanisms, HIV-induced dementia, multiple sclerosis, and Alzheimer's disease (AD).[8–11]

Vascular dystrophy has been shown to be involved in the deposition of the amyloid beta-protein in the brains of AD. Although the mechanism remains undiscovered, it has, however, been shown that more numerous deposits of A beta 40 and A beta 42 can be found in the brains of Alzheimer's patients than in non-demented controls. Together with evidence of no difference in the level of A beta 40 and A beta 42 in peripheral sera between AD and controls, it is suggested that a dysfunction of the BBB could induce abnormal transport of A beta from sera, and accumulation, into the CNS, playing a critical role in the development of AD.[11–16]

The aging of the central nervous system and the development of incapacitating neurological diseases, such as AD, is associated with a wide spectrum of histological and pathophysiological changes eventually leading to a diminished cognitive status. Various forms of cerebrovascular insufficiency, such as reduced blood supply to the brain or disrupted microvascular integrity, may occupy an initiating or intermediate

position in the sequence of events ending with cognitive malfunction. Although the diverse triggers and stages of neuro-degenerative processes are incompletely defined, the contribution of cerebrovascular deficiencies has become recognized as an important, if not a necessary, antecedent.

We hypothesize that BBB dysfunction may contribute to the development of overlapping and disabling cerebrovascular conditions that include microvascular hemorrhage and dementia. This hypothesis could explain the link between ischemic cerebral small-vessel disease and several apparently clinically distinct dementia syndromes. This hypothesis is supported by pathological, epidemiological, and experimental studies in lacunar stroke and examinations of the BBB with magnetic resonance imaging (MRI).[17] We believe that the significance of BBB dysfunction as an early neurophysiologic cascading step leading to disabling brain diseases has been underappreciated.

Confirmation that blood-brain barrier failure plays an essential and rate-limiting step to CNS disease processes could provide a target for new treatments to reduce the effects of vascular disease on the brain and prevent or reduce cognitive decline and dementia.[18]

With regards,

Jim Sondecker, BS, MS
President, Behavioral Health Services
Stockton, California

Michael Smith, MD
Medical Director, Behavioral Health Services
Stockton, California

Dave Robinson, DO
St. Joseph's Medical Center
Stockton, California

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